Photo by Sylvia Pecota

'Fatigue'.

THE IMPACT OF CAFFEINE ON COGNITIVE AND PHYSICAL PERFORMANCE AND MARKSMANSHIP DURING SUSTAINED OPERATIONS

by Tom M. McLellan, Doug G. Bell, Harris R. Lieberman and Gary H. Kamimori

Recent military operations have shown the importance of sustaining operational capabilities throughout the day and night for prolonged periods of time. Such a requirement inevitably leads to various states of sleep deprivation in very stressful environments. It is well documented that sleep loss impairs cognitive performance,[1] and both physical and cognitive performance alone or in combination are critical for the successful outcome across the full spectrum of military operations. Cognitive performance will be degraded with less than 7 hours of sleep in each 24 hours.[2] If 4 to 7 hours of sleep are obtained within every 24-hour period, cognitive performance will stabilize at a lower level, and with less than 4 hours of sleep in every 24 hours, cognitive performance will degrade continuously and rapidly over days with no stabilization.[3] Physical performance is more resistant to sleep deprivation,[4,5] but nonetheless those physical tasks that involve self-pacing and motivational efforts to continue are affected by sleep deprivation.[6,7] Military guides have been developed to assist commanders in the management of cognitive fatigue during periods of sleep deprivation,[8] but these guides have not considered in detail the impact of intervention strategies that could be used to optimize both cognitive and physical performance.

This paper reports on the use of caffeine as a possible intervention strategy to enhance mission effectiveness during sustained operations. The paper summarizes the research efforts of defence scientists in Canada and the United States, and a collaborative programme within The Technical Cooperation Program (TTCP) involving Australia, New Zealand and the United Kingdom as well.

CAFFEINE

Caffeine is a behaviourally active food constituent and drug that is naturally present in many popular foods. Its use is widely accepted in our society, and its use is commonplace within the military community. Coffee, tea and colas all contain caffeine and are popular in many countries throughout the world. Although the levels of caffeine in foods vary greatly, coffee typically contains the most caffeine, with about 65-110 mg per cup, tea has an intermediate amount with about 40-60 mg per cup, and cola and some other soft drinks have about 40 mg per serving.

Caffeine, which readily crosses the blood-brain barrier, appears to exert its effects on the brain via modulation of adenosine receptors.[9] Functional adenosine receptors are

Dr. Tom McLellan and Douglas Bell *are with the Operational Medicine Section of Defence R&D Canada Toronto.* Dr. Harris Lieberman *is with the Military Nutrition Division of the United States Army Institute of Environmental Medicine in Natick, MA.* Dr. Gary Kamimori *is with the Walter Reed Army Institute of Research, Department of Neurobiology & Behavior, Division of Neuropsychiatry, in Silver Spring, MD.*

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involved in the regulation of arousal level. Caffeine acts as an adenosine receptor antagonist and thus it blocks or reduces the impact of adenosine in those brain neurons that have functional adenosine receptors. If the inhibitory effects of adenosine are reduced then arousal levels will be increased.

COGNITIVE PERFORMANCE

The use of caffeine in military operations was recently reviewed by the Committee on Military Nutrition Research[10] (CMNR) in the United States, who concluded that caffeine, in doses of 100 to 600 mg, can maintain cognitive performance, especially in situations of sleep deprivation. The report was based on research conducted at a number of institutions, including several military laboratories, that demonstrated caffeine consistently improves vigilance in rested volunteers, and has more generalized effects on cognitive performance in sleep-deprived individuals.[11-15]

Defense scientists at the United States Army Research Institute of Environmental Medicine (USARIEM) have conducted a number of studies of caffeine in both rested and sleep-deprived volunteers. Their work has utilized caffeine in moderate doses (up to 300 mg), and often focused on vigilance as a critical dependent measure. The intent of their work was to demonstrate that caffeine had militarily-relevant, beneficial effects on cognitive performance. For example, in non-sleep-deprived military volunteers, vigilance attending to a radar-screen-like display for two hours was significantly improved following the ingestion of a moderate 200 mg dose of caffeine.[16] Johnson & Merullo[17] also demonstrated in a series of studies using a marksmanship simulator with non-sleep-deprived military volunteers that 200 mg of caffeine improved target detection speed without adversely affecting rifle-firing accuracy, as noted in Figure 1.

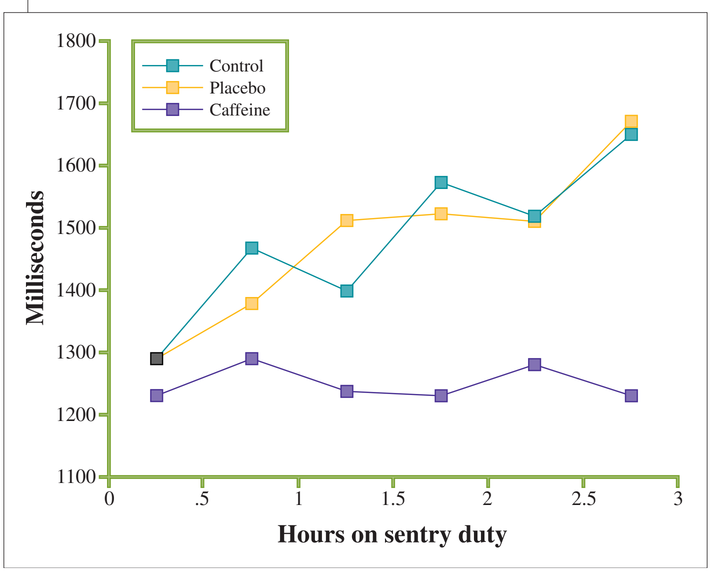

Figure 1 – The effects of 200 mg of caffeine versus either a placebo or a non treatment control condition on target detection response time over 3 hours of a simulated sentry duty task. From Johnson and Merullo, 2000.

Additional work at USARIEM has evaluated the effects of caffeine during severe operational stress and sleep deprivation[18] in US Navy SEAL trainees during an extraordinarily stressful week of training known as 'Hell Week'. During this week, trainees experience the combined stressors of near total sleep deprivation, exposure to cold, continuous, often intense physical activities and extensive psychological stress. For this study, caffeine in doses of 100, 200 and 300 mg, or a placebo, was administered to SEAL trainees after three days of sleep deprivation, and a variety of cognitive tests were administered. Caffeine produced dose-related improvements in visual vigilance, choice reaction time, repeated acquisition (a test of learning and memory), and reduced self-reported fatigue and sleepiness as shown in Figures 2 and 3. The greatest effects of caffeine were measured one hour following ingestion, but significant effects persisted for eight hours. This study demonstrated that even in the most adverse operational circumstances, moderate doses of caffeine had unequivocal, beneficial effects on cognitive performance.

Recently, a caffeine-containing gum has been commercially formulated. Research conducted by the US Army's Walter Reed Army Institute of Research (WRAIR) has demonstrated it is absorbed more rapidly then caffeine in pill form.[19] This unique formulation may be one of several

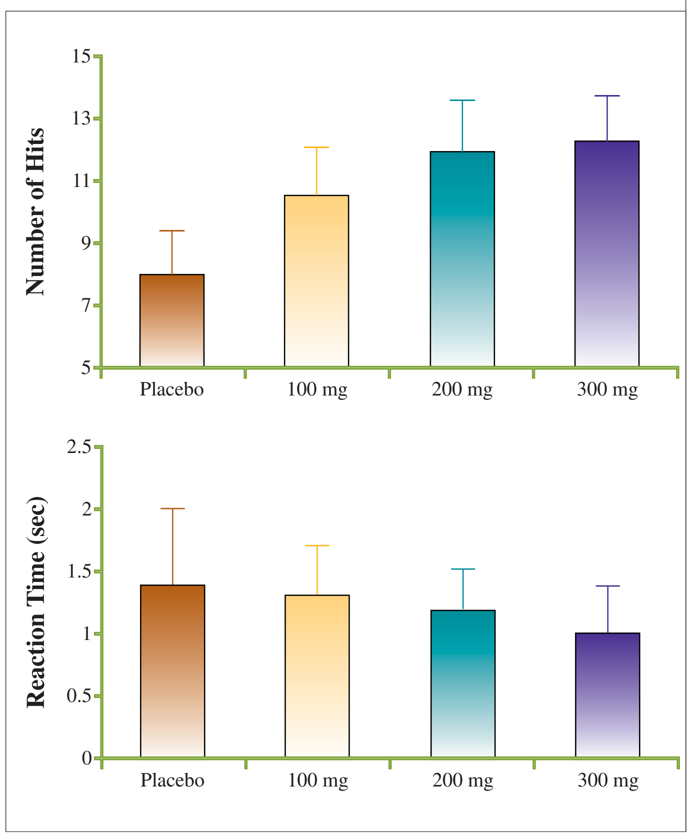

Figure 2 – The effect of caffeine dose on the number of correct hits (maximum of 20) and response time during a visual vigilance task presented during the 73rd hour of 'Hell Week'. Caffeine was ingested 1 hour prior to testing. A dose response effect for caffeine was observed with values obtained following the ingestion of 300 mg being significantly different from placebo. From Lieberman et al., 2002.

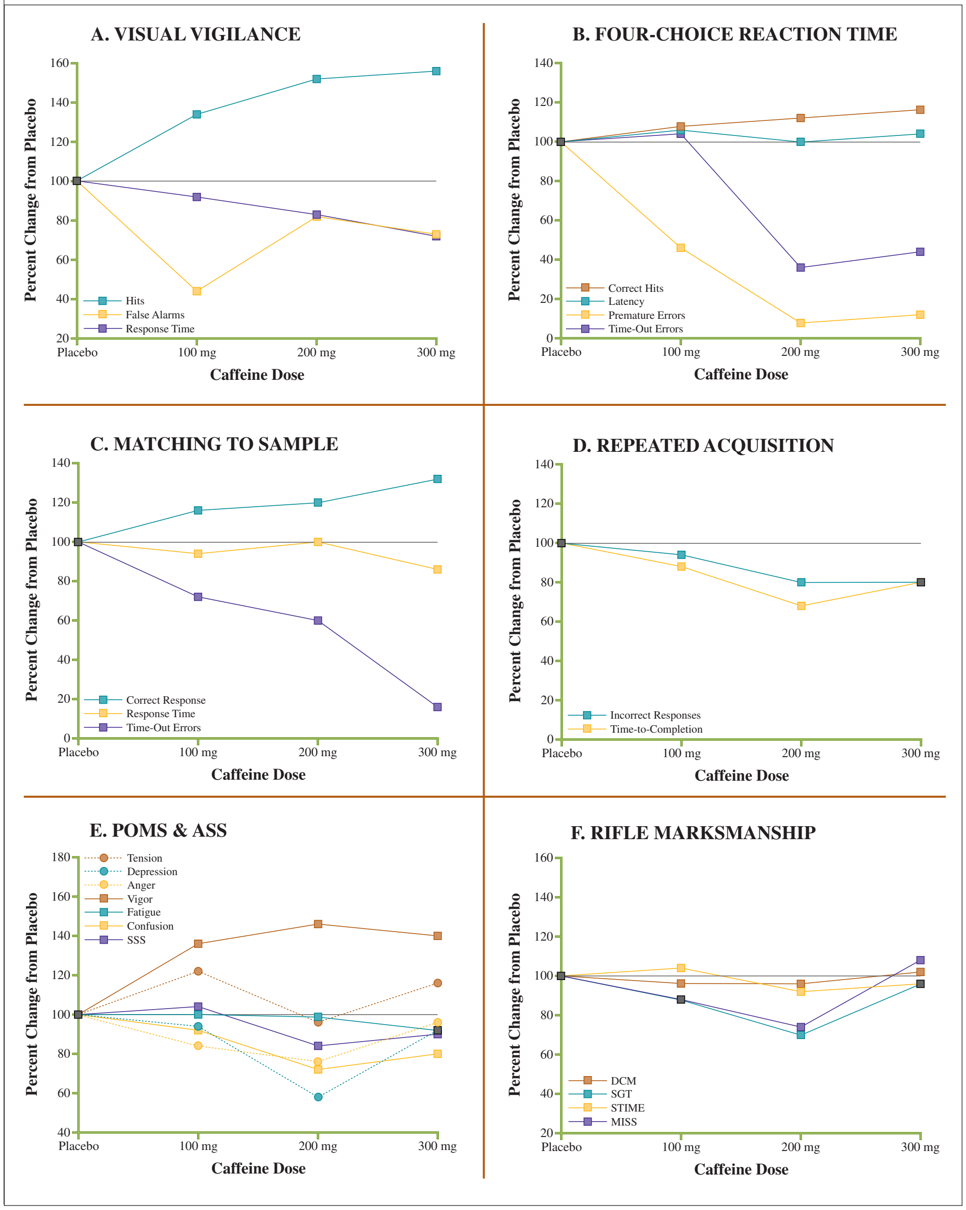

Figure 3 – Percent change in performance and mood following varying doses of caffeine compared to placebo treatment at the 73rd hour of 'Hell Week'. Caffeine was ingested 1 hour prior to testing. A. Percent change from placebo on measures of visual vigilance. B. Percent change from placebo on the four choice visual reaction time test. C. Percent change from placebo on a matching-to-sample test of visual memory. D. Percent change on a repeated acquisition test, which assesses motor learning and memory. E. Percent change from placebo on two mood questionnaires, the Profile of Mood States (POMS) and the Stanford Sleepiness Scale (SSS). F. Percent change from placebo on measures of rifle marksmanship. From Lieberman et al., 2002.

that could be used in military operations, and is the one that is currently being used in our TTCP collaborative effort. Studies conducted at WRAIR have shown that 200 mg doses of caffeine administered at 0300, 0500 and 0700 hours are effective for maintaining cognitive function during a night of sleep deprivation.[20] Data from this study have also demonstrated that blood levels of caffeine were maintained using the two-hour dosing paradigm.[21] Subsequent unpublished work from WRAIR has shown that repeated 300 mg doses, at two-hour intervals, to a total dose of 900 mg were effective during a night without sleep in 16 military personnel who were either low (<100 mg/day) or high (>400 mg/day) habitual users of caffeine. Subjects in this study participated in four separate trials with a placebo and with 100, 200, or 300 mg doses in a double-blind cross over design. There were no reports of significant side effects in any of the subjects at any of the tested doses.

It has been suggested that caffeine's positive effects on cognitive function will be reduced as users become tolerant to its effects. However, most of the studies reported above were in individuals who were regular users of caffeine, and who were not restricted from caffeine use except immediately prior to testing. In addition, in several studies where the habitual caffeine use of volunteers has been assessed, there is little or no difference in performance following caffeine administration as a function of prior caffeine consumption history.[22,23]

There are, of course, adverse effects associated with caffeine consumption in high doses. Caffeine administration can increase anxiety and unsteadiness, but these effects only seem to occur at doses that are higher than those typically consumed in foods.[24] Further, in the study conducted with Navy SEAL trainees, it was found that fine motor control (hand steadiness) as assessed by a marksmanship simulator, was actually improved by administration of caffeine at moderate doses.[25] Although improvement in marksmanship was evident following caffeine ingestion in sleep-deprived individuals, i.e., the Navy SEAL trainees, recent evidence has shown that marksmanship is not improved in rested individuals[26] following the ingestion of 300 mg of caffeine. However, it is important to emphasize that marksmanship was not impaired following caffeine ingestion for the rested soldiers.

Thus, caffeine's effects on marksmanship may be more evident during periods of sustained operations when sleep loss is inevitable. It is also known that high doses and long acting forms of caffeine are particularly likely to interfere with sleep,[27] so when the drug is used operationally this must be taken into consideration.

Nutritional neuroscience has only recently begun to coalesce as a separate, identifiable area of scientific inquiry. In the United States, caffeine is considered a nutritional

supplement. Military scientists in the US, in part because nutritional interventions are less controversial and more widely applicable than drugs, have conducted considerable research on the cognitive effects of various nutrients, food constituents and dietary supplements. The greatest progress has been made with regard to caffeine, with an American review panel, the CMNR, recommending it be employed as the "compound of choice for counteracting cognitive deficits"[28] during military operations.

PHYSICAL PERFORMANCE

The scientific literature also contains many reports on the efficacy of caffeine use to enhance physical performance and these are summarized in a recent review.[29] Findings are equivocal and depend on the type of exercise used to evaluate the effects of the drug, the dose of the drug ingested, and whether the subjects were regular consumers of caffeine. For exercise tests involving running or cycling to exhaustion, improvements are in the order of 25 to 35 percent compared with the taking of a placebo.[30-36] However, typically these studies have been concerned about the use of caffeine in an athletic arena involving a single dose of the drug and subsequent performance[37-41] or repeated dosing of the drug over several hours during a single prolonged competition or period of exercise.[42,43]

For the military, however, physical challenges may occur repeatedly over one day or several days of sustained operations. Thus, several questions had to be addressed before appropriate guidelines could be recommended for the use of the drug in an operational setting. For example, it becomes critical to understand how long the ergogenic effect of a single dose of caffeine will last, so that strategies for efficacious re-dosing can be developed. Military operations may be delayed or cancelled at the last minute, and information about the time course of the effect of caffeine would assist in the planning and subsequent rescheduling of activities. Further, it is important to know whether these re-dosing strategies would be different for users and non-users of the drug, and whether habitual users of caffeine require higher doses to obtain the same benefits.

As stated earlier, caffeine acts as an adenosine receptor antagonist. Regular consumption of caffeine is associated with an up-regulation of the number of these adenosine receptors in the vascular and neural tissues of the brain.[44,45] One might expect, therefore, that users and non-users of caffeine would respond differently to the same dose of the drug, since it is known that some individuals are more sensitive than others to caffeine.[46] A third issue focuses on the recent findings reported by Graham et al.[47] that coffee does not provide the same ergogenic effect as an equal bolus of anhydrous caffeine. Since many military personnel are consumers of coffee, it is essential to determine whether the consumption of repeated cups of coffee would antagonize the subsequent benefits that follow the ingestion of anhydrous caffeine delivered in a gum or capsule.

The first two questions have recently been addressed by Bell and McLellan.[48] They examined 13 caffeine users and eight non-users of the drug during exercise to exhaustion at 80 percent of their maximal aerobic power one, three and six hours after a bolus dose of anhydrous caffeine (5 mg/kg delivered in capsules) was ingested. Three important findings from this study are shown in Figure 4. First, caffeine was effective for enhancing exercise performance in both groups. Second, the improvement was greater in the non-users, and third, this improvement lasted longer in the non-users, with positive effects still evident six hours after the ingestion of the drug. The fact that blood concentrations of caffeine were significantly reduced six hours after ingestion compared with the trials conducted earlier, implied that a threshold concentration was required to exert a positive effect. Further, the findings suggested that this threshold concentration was different for users and non-users of the drug.

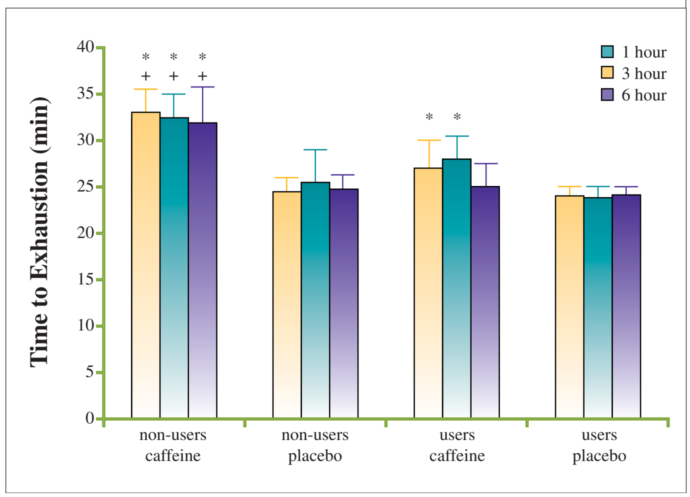

Figure 4 – Time to exhaustion at 80% maximal physical work capacity in caffeine users and non-users 1, 3 and 6 hours after caffeine ingestion. *Caffeine > Placebo. + Non-users > Users. From Bell and McLellan, 2002.

The intent of a subsequent study was to determine whether restoring blood concentrations to values above a threshold level would again be associated with an improvement in exercise endurance for users of the drug.[49] In this study, subjects exercised to exhaustion once in the morning and five hours later in the afternoon. One hour before each exercise test, caffeine or placebo capsules were administered. During Trial A subjects received a 5 mg/kg dose of caffeine in the morning, and a smaller 2.5 mg/kg dose of the drug in the afternoon. Trial B represented placebo capsules in the morning and afternoon, Trial C a 5 mg/kg dose of caffeine in the morning only, and Trial D a 5 mg/kg dose of the drug in the afternoon. Figure 5 shows the caffeine concentrations in the plasma. Clearly, blood concentrations were maintained at high levels during the morning and afternoon for Trial A, but had decreased to lower values during the afternoon of Trial C that involved placebo capsules prior to the second test. However, as shown in Figure 6, the different plasma concentrations of caffeine for these trials did not have a differential impact on performance. The findings revealed that although similar high plasma concentrations of caffeine maintained the ergogenic effects of the drug during repeated exhaustive exercise (Trial A), a lower plasma concentration prior to the second exercise test was not

associated with a loss of the ergogenic effect of the drug (Trial C). The data also showed that the ergogenic effect that follows caffeine ingestion can occur at lower plasma concentrations during a subsequent bout of exhaustive exercise in the afternoon (Trial D).

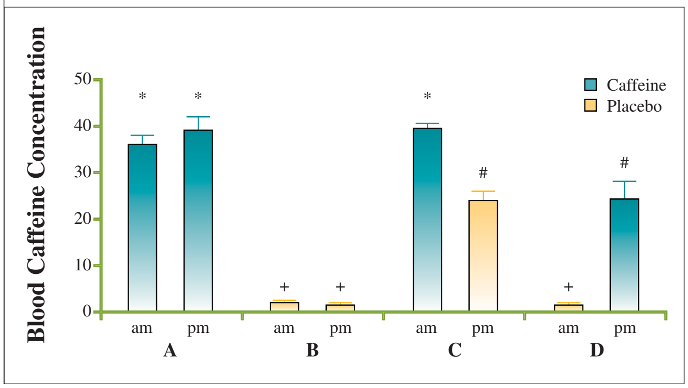

Figure 5 – Caffeine plasma concentrations after 10 minutes of exercise at 80% of maximal physical work capacity. * + # Symbols indicate similar means. From Bell and McLellan, 2003.

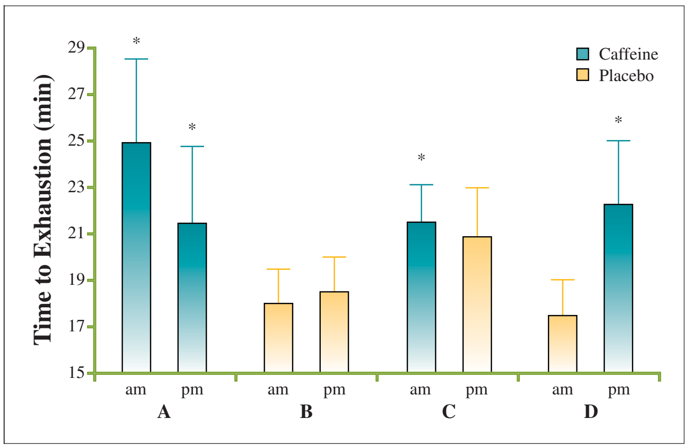

Figure 6 – Time to Exhaustion at 80% of maximal physical work capacity. * Significantly different from B (am,pm) and D (am). From Bell and McLellan, 2003.

What are the implications of these findings for military personnel involved with repeated exercise bouts at different times of the day? First, performing exhaustive exercise for 20 to 30 minutes in the morning does not adversely affect the endurance during the same task five hours later in the afternoon. Thus, scheduling of military operations could involve repeated exhaustive exercise bouts separated by at least five hours of recovery. Second, the ingestion of a second smaller dose of caffeine prior to the performance of a second exhaustive exercise bout is not necessary to maintain the 20 to 30 percent improvement in time to exhaustion that follows ingestion of a higher dose of the drug in the morning. In fact, this additional dose of the drug has a tendency to adversely affect endurance.

We would speculate that the initial exercise bout alters one's sensitivity to circulating levels of caffeine such that the ergogenic effect of the drug on a successive bout of exercise is evident much longer than was previously reported for a single bout of exercise.[50] We do not know for how long this altered sensitivity might last, and whether this would be different between users and non-users of the drug. These are questions that require further investigation. However, based on our previous findings[51] we would still advocate re-dosing with caffeine for users of the drug five hours following an initial 5 mg/kg dose if prior exercise did not occur.

The issue about the effects of coffee versus anhydrous caffeine has gained interest because of the recent findings reported by Graham et al.[52] Since most users of caffeine obtain the source of the compound from coffee, it is important to know whether the consumption of coffee would provide the same ergogenic benefit as the ingestion of anhydrous caffeine in capsule or gum form. Graham et al.[53] showed that running time to exhaustion at 80 percent of maximal physical capacity following the ingestion of anhydrous caffeine in capsules was improved 31 percent when compared to placebo capsules, and 23 percent when compared to decaffeinated coffee ingestion. However, when similar blood concentrations of caffeine were achieved, following the ingestion of coffee or anhydrous caffeine dissolved in decaffeinated coffee, performances were not improved. The latter findings suggested that some other component(s) common to both coffee and decaffeinated coffee alter adenosine receptor sensitivity to circulating levels of caffeine and suppress the ergogenic effect.

Most coffee drinkers do not consume the equivalent volume of 3 or 4 cups of coffee at one time. Rather, they may consume several cups of the beverage throughout the day. Thus, a more pertinent question to address is whether the consumption of one cup of coffee antagonizes or improves the ergogenic effects that follow the ingestion of anhydrous caffeine. Recent work from DRDC–Toronto[54] has addressed this question. Exercise time to exhaustion at 80 percent of maximal aerobic power was assessed one hour following the ingestion of various doses of anhydrous caffeine in capsule form that followed the consumption of one cup of regular or decaffeinated coffee. Results are presented in Figure 7. The findings clearly

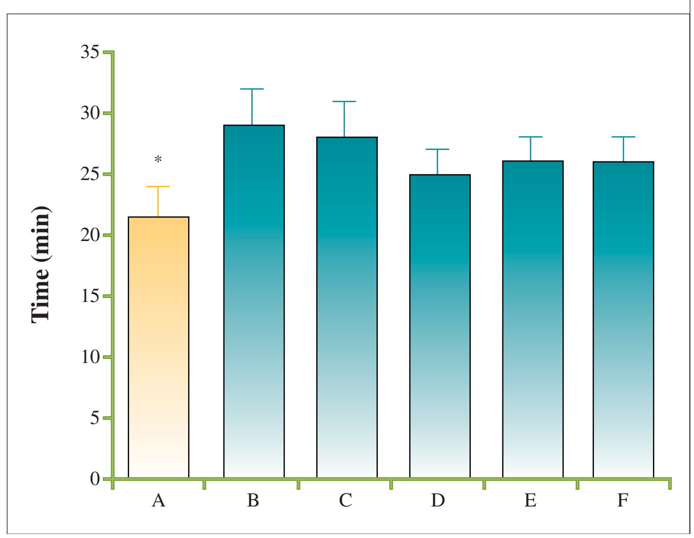

Figure 7 – Time to exhaustion at 80% of maximal physical work capacity following the consumption of decaffeinated coffee (DECOF), regular coffee (COF) or coloured water together with varying doses of anhydrous caffeine (CAF). * Significantly different from all other treatments. A = DECOF + Placebo, B = DECOF + CAF (5 mg/kg), C = COF + CAF (5 mg/kg), D = COF + CAF (3 mg/kg), E = COF + CAF (7 mg/kg), F = coloured water + CAF (5 mg/kg). From Bell and McLellan, 2003.

revealed that the consumption of one cup of regular or decaffeinated coffee had no impact (positive or negative) on the ergogenic effect that followed the ingestion of 5 mg/kg of anhydrous caffeine in capsule form. An important question that does remain to be answered is whether multiple cups of coffee consumed over several hours have a negative impact on the effect of anhydrous caffeine consumed prior to the performance of exhaustive exercise.

COLLABORATIVE EFFORTS

Under the umbrella of TTCP, a collaborative research program has been initiated focusing on the application of caffeine during sustained operations to enhance physical and cognitive performance and marksmanship. A laboratory-based trial was just completed which simulated a night-time infantry mission. Soldiers completed a 28-hour period of sleep deprivation that began at 0700 hours and concluded the next morning at 1100. Beginning at 2200 hours of the first evening, soldiers began the night-time mission scenario by completing a two-hour forced march followed by 45 minutes of sandbag piling to simulate the establishment of a defensive position. From 0100 to 0500 hours of the second morning, cognitive performance was assessed with a variety of tasks. From 0500 to 0700 hours marksmanship was recorded with a small arms training simulator. A final physical challenge to simulate movement to an evacuation point was conducted between 0700 and 0800 hours, with additional cognitive tests being performed for the remaining three hours of the trial. Preliminary unpublished data have shown that the use of the caffeine significantly improved the soldiers' ability to complete the physical and cognitive challenges that were presented throughout the night and improved vigilance and accuracy of marksmanship.

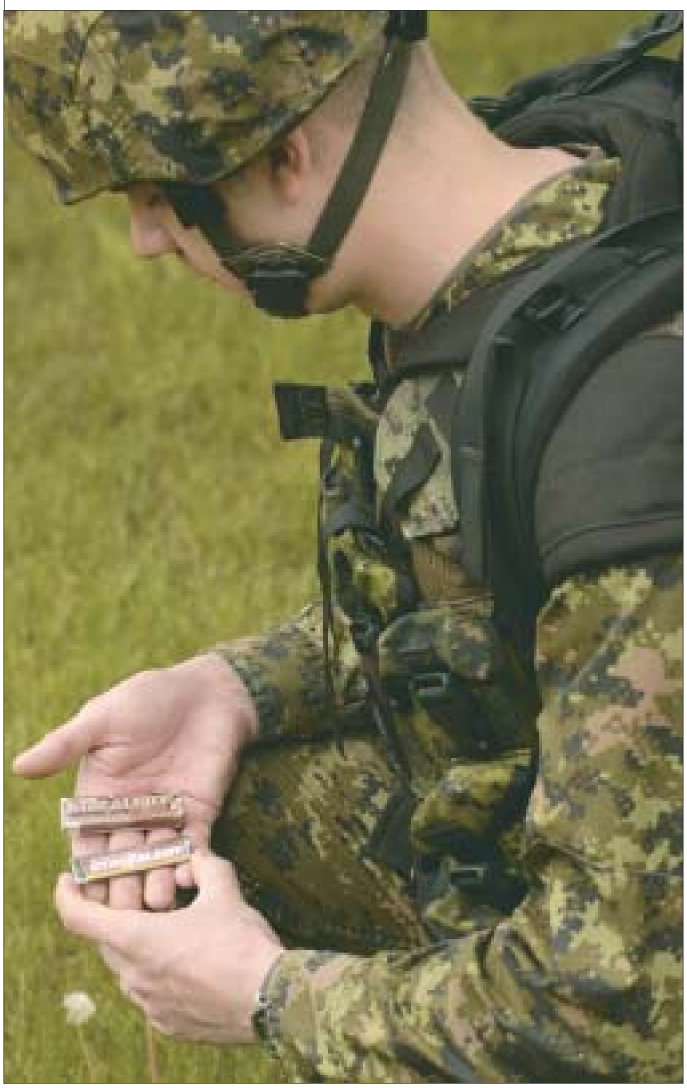

Figure 8 – An example of the Caffeine Gum that could be used to enhance physical and cognitive performance.

Presently, our collaborative efforts have focused on use of a caffeinated gum produced in the US to deliver caffeine because it produces rapid entry into the circulation via the highly vascular tissues in the mouth. Each pack contains five 100 mg sticks of caffeinated gum, as shown in Figure 8.

Defence scientists from both Canada and the United States have generated recommendations for the use of this gum to enhance cognitive and physical performance during rested and sleep deprived states. These recommendations are presented below and have been abbreviated on laminated cards (Figure 9) for quick and easy reference by field commanders.

RECOMMENDATIONS FOR USE OF CAFFEINATED GUM

Chewing one or two sticks of gum for five minutes, then discarding, has been shown to deliver 85 percent of the total caffeine dose in each stick. Each stick contains 100 mg of caffeine.

1. ***For mental performance:*** In a rested state, start with one stick and chew more as needed to maintain alertness. In a sleep deprived state, no more than two sticks every two hours for up to six hours should be consumed.

2. ***For physical performance:*** Chew two sticks for five minutes followed immediately by another two sticks prior to beginning the initial activity. Re-dose with one stick after six hours for subsequent hard work.

3. ***Physical followed by mental performance:*** Use four sticks initially for physical performance prior to initial assault. To maintain cognitive performance after the physical effort, chew one stick as required.

STAY ALERT CAFFEINE GUM

Why Use This Product

- Caffeine gets in faster
- Fewer side effects
- Easy to use

DEFENCE DÉFENSE
DRDC Toronto

How to Use for Performance

(Chew no more than 2 sticks at a time for 5 minutes.)

Mental:
- Rested: 1 stick as required
- Sleep deprived: 2 sticks every 2 hr for 6 hr

Physical:
- Rested/Sleep deprived : 3-4 sticks initially, 1 additional stick after 6 hr

Combined Physical/Mental:
- as above for physical, re-dosing with 1 stick as needed for mental alertness

DO NOT USE THIS PRODUCT IF YOU ARE OVERLY SENSITIVE TO CAFFEINE

Figure 9 – Front and back of the card explaining the use of the caffeine gum.

4. ***Mental followed by physical performance:*** In the rested state, chew a total of four sticks within two hours of the exercise. In the sleep-deprived state, where multiple sticks of gum would already have been chewed within a four-hour period, additional sticks of gum may not be required for optimizing physical performance.

5. Regular caffeine users may have to slightly increase their dose to achieve the same benefits.

6. Do not exceed 10 sticks in a 24-hour period.

"...Caffeine, in doses of 100 to 600 mg, can maintain cognitive performance, especially in situations of sleep deprivation."

SUMMARY

Current doctrine requires soldiers to sustain operational effectiveness for 24 hours a day continuously for several days. Inevitably, both cognitive and physical performance will deteriorate because of sleep loss. Because of its documented ability to enhance cognitive and physical performance during both rested and sleep-deprived states, caffeine can be of use during military operations. The use of caffeine has minimal side effects and its use as a drug (as defined in Canada) is well tolerated and accepted within the military community.

The use of caffeine to enhance military effectiveness does not simply mean drink lots of coffee. There are important research questions that still need to be addressed. For example, issues pertaining to the timing of dosing and re-dosing strategies and the dose response relationships for users and non-users of caffeine need to be clarified. Also, the persistence of the altered sensitivity from prior exercise and how this impacts caffeine's effects on cognitive performance, and whether the consumption of coffee over several hours antagonizes the effects of anhydrous caffeine are additional studies that need to be completed. Answers to these questions will increase our understanding of the mechanisms of action of caffeine — information that will ultimately be beneficial for its use during military operations.

ACKNOWLEDGEMENTS

Human volunteers participated after giving their free and informed consent. This research was conducted in conformity with AR 70-25, USAMRDC Reg 70-25 on the use of human volunteers in research, and the "Guiding Principles for Research Involving Animals and Human Beings". Use of trade names does not constitute endorsement of product. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the opinions of the Department of National Defence, the United States Department of the Army or the United States Department of Defense.

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"...Even in the most adverse operational circumstances, moderate doses of caffeine had unequivocal, beneficial effects on cognitive performance."

NOTES

1. G. Belenky, N. J. Wesensten, D. R. Thorne, et al., "Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study." *J Sleep Res.* 12, 2003, pp.1-12.
2. *Ibid.*
3. *Ibid.*
4. M.J. Plyley, R.J. Shephard, G.M. Davis et al., "Sleep deprivation and cardiorespiratory fitness." *Eur J Appl Physiol.* 56, 1987, pp. 338-344.
5. J.D. Symons, T. Vanhelder, and W.S. Myles, "Physical performance and physiological responses following 60 hours of sleep deprivation." *Med Sci Sports Exerc.* 20, 1988, pp. 374-380.
6. B.J. Martin, "Effect of sleep deprivation on tolerance of prolonged exercise." *Eur J Appl Physiol.* 47, 1981, pp. 345-354.
7. C.D. Rodgers, D.H. Paterson, D.A. Cunningham et al., "Sleep deprivation: effects on work capacity, self-paced walking, contractile properties and perceived exertion." *Sleep.* 18, 1995, pp. 30-38.
8. A.S. Rogers, K.A. Robertson, and B.M. Stone, "The management of irregular work/rest schedules." *A Reference Guide for Commanders.* CG/WORKANDREST/v2.0/MAR2001, DERA Report No. DERA/CHS/PPD/CR010198, Defence Evaluation and Research Agency, UK, 2001.
9. B.B. Fredholm, K. Battig, J. Holmen, et al., "Actions of caffeine in the brain with special reference to factors that contribute to its widespread use." *Pharmacol Rev*. 51, 1999, pp. 83-133.
10. Committee on Military Nutrition Research, F. a. N. B., Institute of Medicine. *Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations.* Washington D.C.: National Academy Press, 2001, pp. 1-157.
11. H.R. Lieberman, R. J. Wurtman, G. G. Emde, et al., "The effects of caffeine and aspirin on mood and performance." *J Clin Psychopharmacol.* 7, 1987, pp. 315-320.
12. D.H. Penetar, U. McCann, D. Thorne, et al., "Effects of Caffeine on Cognitive Performance Mood and Alertness in Sleep-deprived Humans." In: *Food Components to Enhance Performance* Washington D.C.: National Academy Press, 1994, pp. 407-431.
13. C.A. Amendola, J. D. E. Gabrieli, and H. R. Lieberman, "Caffeine's effect on Performance and Mood are Independent of Age and Gender." *Nutritional Neuroscience.* 1, 1998, pp. 269-280.
14. G.H. Kamimori, C. S. Karyekar, R. Otterstetter, et al., "The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers." *Int J Pharm.* 234, 2002, pp. 159-167.
15. H.R. Lieberman, W. J. Tharion, B. Shukitt-Hale, et al., "Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training." *Psychopharmacology (Berl).* 164, 2002, 250-261.
16. B.J. Fine, J. L. Kobrick, H. R. Lieberman, et al., "Effects of caffeine or diphenhydramine on visual vigilance." *Psychopharmacology (Berl).* 114, 1994, pp. 233-238.
17. R.F. Johnson and D. J. Merullo, "Caffeine, Gender, and Sentry Duty: Effects of a Mild Stimulant on Vigilance and Marksmanship." *Pennington Center Nutrition Series Volume 10: Countermeasures for Battlefield Stressors.* K. Friedel, H. R. Lieberman, D. H. Ryan, and G. A. Bray (Eds.) Baton Rouge: Louisiana State University Press, 2000, pp. 272-289.
18. Lieberman et al., 2002, pp. 250-261.
19. Kamimori et al., 2002, pp. 159-167.
20. G.H. Kamimori, D. Johnson, D. Thorne, et al., "Efficacy of multiple caffeine doses for maintenance of vigilance during early morning operations." *Sleep.* 26, 2003, pp. A196.
21. S.A. Syed, G.H. Kamimori, D.A. Johnson, et al., "Multiple dose pharmacokinetics of caffeine administered in chewing gum to normal healthy volunteers." *Int J Clin Pharmacol.* 2003, in review.
22. Fine et al., 1994, pp. 233-238.
23. H.J. Smit and P.J. Rogers, "Effects of low doses of caffeine on cognitive performance, mood, and thirst in low and high caffeine consumers." *Psychopharmacology.* 152, 2000, pp. 167-173.
24. A. Smith, "Effects of caffeine on human behavior." *Food Chem Toxicol.* 40, 2002, pp. 1243-55.
25. W.J. Tharion, B. Shukitt-Hale, and H. R. Lieberman, "Caffeine effects on marksmanship during high-stress military training with 72 hour sleep deprivation." *Aviat Space Environ Med.* 74, 2003, pp. 309-314.
26. R. Gillingham, A.A. Keefe, J. Keillor et al., "Effect of Caffeine on Target Detection and Rifle Marksmanship." *Ergonomics.* Accepted for publication, 2003.
27. Smith, 2002, pp. 1243-55.
28. Committee on Military Nutrition Research, 2001, pp. 1-157.
29. T.E. Graham, "Caffeine and Exercise Metabolism, Endurance and Performance." *Sports Med.* 31, 2001, pp. 785-807.
30. G.R. Cox, B. Desbrow, P.G. Montgomery et al., "Effect of different protocols of caffeine intake on metabolism and endurance performance." *J Appl Physiol.* 93, 2002, pp. 990-999.
31. B. Falk, R. Burstein, I. Ashkenazi et al., "The effect of caffeine ingestion on physical performance after prolonged exercise." Eur *J Appl Physiol.* 59, 1989, pp. 168-173.
32. T.E. Graham and L. L. Spriet, "Performance and metabolic responses to a high caffeine dose during prolonged exercise." *J Appl Physiol.* 71, 1991, pp. 2292-2298.
33. T.E. Graham and L.L. Spriet, "Metabolic, catecholamine, and exercise performance responses to various doses of caffeine." *J Appl Physiol.* 78, 1995, pp. 867-874.
34. M.H. Van Soeren and T.E. Graham, "Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal." *J Appl Physiol.* 85, 1998, pp. 1493-1501.
35. T.E. Graham, E. Hibbert and P. Sathasivam, "Metabolic and exercise endurance effects of coffee and caffeine ingestion." *J Appl Physiol.* 85, 1998, pp. 883-889.
36. W.J. Pasman, M.A. van Baak, A.E. Jeukendrup et al., "The effect of different dosages of caffeine on endurance performance time." *Int J Sports Med.* 16, 1995, pp. 225-230.
37. Graham and Spriet, 1991, pp. 2292-2298.
38. Graham and Spriet, 1995, pp. 867-874.
39. Van Soeren and Graham, 1998, pp. 1493-1501.
40. Graham, Hibbert and Sathasivam, 1998, pp. 883-889.
41. Pasman et al., 1995, pp. 225-230.
42. Cox et al., 2002, pp. 990-999.
43. Falk et al., 1989, pp. 168-173.
44. B.B. Fredholm, "Astra Award Lecture. Adenosine, adenosine receptors and the actions of caffeine." *Pharmacol Toxicol.* 76, 1995, 93-101.
45. Fredholm et al., 1999, pp. 83-133.
46. A. Nehlig, J. L. Daval and G. Debry, "Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects." *Brain Res Brain Res Rev.* 17, 1992, pp. 139-170.
47. Graham, Hibbert and Sathasivam, 1998, pp. 883-889.
48. D.G. Bell and T. M. McLellan, "Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers." *J Appl Physiol.* 93, 2002, pp. 1227-1234.
49. D.G. Bell and T. M. McLellan, "Effect of repeated caffeine ingestion on repeated exercise endurance." *Med Sci Sports Exerc.* 35, 2003, pp. 1348-1354.
50. Bell and McLellan, 2002, pp. 1227-1234.
51. *Ibid.*
52. Graham, Hibbert and Sathasivam, 1998, pp. 883-889.
53. *Ibid.*
54. D.G. Bell and T. M. McLellan. "Exercise performance after coffee and caffeine ingestion." *Med Sci Sports Exerc.* 2003, in review.